General

Guideline Title

Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation.

Bibliographic Source(s)

Sung L, Robinson P, Treister N, Baggott T, Gibson P, Tissing W, Wiernikowski J, Brinklow J, Dupuis LL. Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation. BMJ Support Palliat Care. 2015 Mar 27;:1-10. [50 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Strength of recommendations (Strong, Weak) and quality of evidence (High, Moderate, Low, Very Low) are defined at the end of the "Major Recommendations" field.

Health question: What prophylactic interventions are effective at preventing or reducing the severity of oral and oropharyngeal mucositis in children (0–18 years) receiving treatment for cancer or undergoing haematopoietic stem cell transplantation (HSCT)?

Recommendations

- *Recommendation 1.1*: The Guideline Development Group suggests that cryotherapy may be offered to cooperative children receiving chemotherapy or HSCT conditioning with regimens associated with a high rate of mucositis. (Weak Recommendation, Moderate Quality Evidence)
  Remarks: This recommendation places high value on the possible reduction in mucositis with an intervention with a low risk of harm. It is a weak recommendation because of the lack of paediatric-specific evidence, because the majority of studies that demonstrated the benefit of cryotherapy were conducted using chemotherapy regimens not commonly given to children and because of the methodological limitations of the conducted trials. Regimens appropriate for cryotherapy are restricted to agents with a short infusion time and a short half-life.
- *Recommendation 1.2*: The Guideline Development Group suggests that low-level light therapy may be offered to cooperative children receiving chemotherapy or HSCT conditioning with regimens associated with a high rate of mucositis. (Weak Recommendation, High Quality Evidence)
  Remarks: This recommendation places high value on the possible reduction in mucositis with an intervention with a low risk of harm. It is a

weak recommendation because this strategy requires specialised equipment and expertise and it is unknown whether it is feasible to deliver this therapy modality in routine clinical practice, particularly in a paediatric population. The ideal treatment parameters and cost-effectiveness of this approach are unknown.

- *Recommendation 1.3*: The Guideline Development Group suggests that keratinocyte growth factor (KGF) may be offered to children receiving HSCT conditioning with regimens associated with a high rate of severe mucositis. (Weak Recommendation, High Quality Evidence)
  Remarks: This recommendation places high value on the evidence of efficacy of KGF in adult populations. It is a weak recommendation because of the lack of efficacy and toxicity data in children, a theoretical concern that young children may be at increased risk of adverse effects related to mucosal thickening and the lack of long-term follow-up data in paediatric cancers.

Definitions

Quality of Evidence

High Quality	Further research is very unlikely to change confidence in the estimate of effect.
Moderate Quality	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low Quality	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low Quality	Any estimate of effect is very uncertain.

Strength of Recommendations

Strong Recommendation	When using Grading of Recommendations Assessment, Development and Evaluation (GRADE), panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak Recommendation	Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Clinical Algorithm(s)

An algorithm titled "Suggested implementation approach for the prevention of oral mucositis guideline recommendations" is provided in the original guideline document.

Scope

Disease/Condition(s)

Oral and oropharyngeal mucositis

Note: For the purpose of the guideline, oesophageal mucositis is encompassed by the terms oral and oropharyngeal mucositis; these conditions are referred to as oral mucositis in the guideline for the sake of brevity. The Guideline Development Group has explicitly excluded lower gastrointestinal mucositis from the scope of the guideline.

Guideline Category

Prevention

Clinical Specialty

Dentistry

Hematology

Oncology

Pediatrics

Intended Users

Advanced Practice Nurses

Dentists

Nurses

Patients

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To develop an evidence-based clinical practice guideline for the prevention of oral and oropharyngeal mucositis in children (0–18 years) receiving treatment for cancer or undergoing haematopoietic stem cell transplantation (HSCT)

Target Population

Children 0 to 18 years of age receiving cytotoxic chemotherapy or radiotherapy for cancer or undergoing haematopoietic stem cell transplantation (HSCT)

Interventions and Practices Considered

1. Cryotherapy
2. Low-level light therapy (LLLT)
3. Keratinocyte growth factor (KGF)

Major Outcomes Considered

- Severe oral mucositis
- Mucositis of any severity
- Pain and adverse events associated with the intervention
- Receipt of opioid analgesia
- Receipt of enteral or parenteral nutrition
- Infection outcomes
- Fever

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Full search strategies can be found in online supplementary appendix 2 (see the "Availability of Companion Documents" field).

Randomized Controlled Trials of Cryotherapy

Search Strategy

The following databases were searched and included articles indexed as of April 1, 2014: Ovid in MEDLINE, EMBASE, and EBM Reviews – Cochrane Central Register of Controlled Trials.

Selection Criteria and Appraisal

Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. The Guideline Development Group included fully-published papers that were RCTs or quasi-RCTs of cryotherapy for the prevention of mucositis in patients receiving treatment for cancer or undergoing HSCT. There was no restriction by language. Two reviewers compiled the evidence summary table.

Randomized Controlled Trials of Low Level Light Therapy (LLLT)

A systematic review of RCTs evaluating LLLT to prevent mucositis in adults and children was recently published.

Search Strategy

The following databases were searched and included articles indexed as of February 17, 2014: Ovid in MEDLINE, EMBASE, EBM Reviews – Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS and LILACS. The search strategies may be found in Oberoi et al. (see the "Availability of Companion Documents" field).

Selection Criteria and Appraisal

Two reviewers independently evaluated the titles and abstracts of publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. Studies were included if the population consisted of patients with cancer or undergoing HSCT and patients were randomly assigned to receive prophylactic LLLT versus placebo, no therapy or usual care. Studies were excluded if: (1) allocation not randomly assigned; (2) absence of a placebo or no treatment group; (3) randomized chemotherapy cycles or left and right buccal mucosa within a patient rather than randomizing patients (as episodes would not be independent); and (4) duplicate publication. Studies included in the meta-analysis were not restricted by language or publication status.

Randomized and Non-Randomized Trials of Keratinocyte Growth Factor (KGF)

Randomized Studies of KGF in Adult and Pediatric Populations

Search Strategy

The following databases were searched and included articles indexed as of April 1, 2014: Ovid in MEDLINE, EMBASE, and EBM Reviews – Cochrane Central Register of Controlled Trials.

Selection Criteria and Appraisal

Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. The Guideline Development Group included fully-published papers that were RCTs or quasi-RCTs of KGF for the prevention of mucositis in patients receiving treatment for cancer or undergoing HSCT. There was no restriction by language. Two reviewers compiled the evidence summary table.

Non-Randomized Studies of KGF Conducted in Pediatric Populations

Search Strategy

The same search strategy to identify RCTs of KGF was used since a filter for trial design was not added.

Selection Criteria and Appraisal

Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. The Guideline Development Group included fully-published papers of any study design that evaluated KGF for the prevention of mucositis in pediatric patients (≤25 years of age) receiving treatment for cancer or undergoing HSCT. There was no restriction by language.

Randomized Controlled Trials of Any Intervention in Pediatric Patients

Search Strategy

The following databases were searched and included articles indexed as of April 1, 2014: Ovid in MEDLINE, EMBASE, and EBM Reviews – Cochrane Central Register of Controlled Trials.

Selection Criteria and Appraisal

Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. The Guideline Development Group included fully-published papers that were RCTs or quasi-RCTs of any intervention for the prevention of mucositis in pediatric patients (≤25 years of age) receiving treatment for cancer or undergoing HSCT. There was no restriction by language. Two reviewers compiled the evidence summary table.

Refer to the "Evidence Identification" section in original guideline document for a discussion of how the Guideline Development Group determined the scope and rationale for the guideline.

Number of Source Documents

Randomized Controlled Trials of Cryotherapy to Prevent Oral Mucositis in Adults and Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation

A total of 390 references were identified from the search strategy. After screening titles and abstracts, 28 were retrieved in full and 16 satisfied the eligibility criteria (14 primary and 2 companion papers).

Randomized Controlled Trials of Low-Level Light Therapy to Prevent Oral Mucositis in Adults and Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation

A total of 2,446 references were identified from the search strategy. After screening titles and abstracts, 57 were retrieved in full and 18 satisfied the eligibility criteria (details available in Oberoi et al. [see the "Availability of Companion Documents" field]).

Randomized Controlled Trials of Keratinocyte Growth Factor to Prevent Oral Mucositis in Adults and Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation

A total of 906 references were identified from the search strategy. After screening titles and abstracts, 25 were retrieved in full and 12 satisfied the eligibility criteria (11 primary and 1 companion paper).

Non-Randomized Controlled trials of Keratinocyte Growth Factor to Prevent Oral Mucositis in Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation

As the search for RCTs of keratinocyte growth factor did not use trial design as a filter, the same 906 references were evaluated. After screening titles and abstracts, 5 were retrieved in full and 4 satisfied the eligibility criteria.

Randomized Controlled trials of Any Intervention to Prevent Oral Mucositis in Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation

A total of 3,873 references were identified from the search strategy. After screening titles and abstracts, 105 were retrieved in full and 24 satisfied the eligibility criteria (21 primary and 3 companion papers).

Appendix 3 (see the "Availability of Companion Documents" field) provides flow charts of the study identification and selection process described above, including reasons for exclusion.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

High Quality	Further research is very unlikely to change confidence in the estimate of effect.
Moderate Quality	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low Quality	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low Quality	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence Synthesis

For all systematic reviews, the Guideline Development Group synthesised the occurrence of severe oral mucositis when at least three studies reported on this outcome for a specific intervention. Severe oral mucositis was defined as World Health Organization (WHO), National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) V.2.0 or Radiation Therapy Oncology Group (RTOG) scale score of 3 or 4. All these scores use a five-point scale ranging from 0 to 4 in which scores of 3 and 4 represent the worst mucositis. The NCI-CTCAE V.3.0 scale ranges from 1 to 5, in which 5 is fatal mucositis. NCI-CTCAE V.3.0 scores of 3–5 were considered severe. All syntheses used the risk ratio (RR) as the effect measure where ratios less than 1 suggest that the intervention is better than placebo or no therapy. The 95% confidence interval (CI) was also described. As they anticipated heterogeneity across studies, a random effects model was used for all analyses. Analyses were conducted using Review Manager (RevMan, V.5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Health Question

The guideline sought to answer the following health question:

- What prophylactic interventions are effective at preventing or reducing the severity of oral and oropharyngeal mucositis in children (0 to 18

years) receiving treatment for cancer or undergoing haematopoietic stem cell transplantation (HSCT)?

Guideline Development Panel

The Pediatric Oncology Group of Ontario (POGO) Mucositis Prevention Guideline Development Group was formed in March 2014 (see online supplementary appendix 1 [see the "Availability of Companion Documents" field]). Members were selected with a view to obtain interdisciplinary representation from internationally recognised experts in paediatric mucositis and POGO institutions.

Decision-Making Process for Formulation of the Recommendations

The Guideline Development Group identified outcomes most important for this guideline. Outcomes of critical importance were severe oral mucositis, mucositis of any severity, pain and adverse events associated with the intervention. Outcomes of lower importance included receipt of opioid analgesia, enteral or parenteral nutrition, infection outcomes and fever, since these outcomes are subject to confounding and institutional variation.

The Guideline Development Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to describe quality of evidence and strength of recommendations. Quality of evidence was evaluated in terms of risk of bias (methodological limitations), imprecision of estimates, inconsistency of results between studies and indirectness (lack of applicability to the target population). In this guideline, indirectness primarily occurred when the data were not paediatric specific. A strong recommendation was made when benefits clearly outweighed the risks and burdens or vice versa. In contrast, a weak recommendation was made when benefits and risks or burdens were closely matched, or when there was considerable uncertainty about the magnitude of the benefits and risks. Each recommendation was carefully deliberated by the panel. Decisions were taken through panel discussions and any differences in opinion were resolved by consensus.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong Recommendation	When using Grading of Recommendations Assessment, Development and Evaluation (GRADE), panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak Recommendation	Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

External Review and Consultative Process

The draft guideline was distributed to 12 external experts in adult and paediatric mucositis. Specific recommendations were reviewed by the panel and the guideline was revised accordingly. The guideline development process took 6 months from constitution of the panel to guideline completion.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of interventions to prevent or reduce the severity of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation (HSCT)

Refer to the "Remarks" sections of the original guideline document for a discussion of the balance between benefits and harms for each of the interventions considered in the guideline.

Potential Harms

- There are two safety considerations with cryotherapy. First, if ice chips are to be used, they may be a choking hazard in very young children, although children who are old enough to comply with cryotherapy are unlikely to be at risk for choking. Second, vasoconstriction of the oral tissues may influence local anticancer activity, although this issue has not been noted in the adult studies.
- In the eight studies reporting that keratinocyte growth factor (KGF) significantly reduced severe oral mucositis, primary toxicities were related to the pharmacological properties of the agent with thickening of the oral mucosa and altered taste sensation. In an allogeneic haematopoietic stem cell transplantation (HSCT) study, toxicities reported included skin rash, skin erythema, altered taste and severe pain in the tongue, buccal mucosa and palate. A case report described a 19-year-old patient who received KGF 60 µg/kg/day for 3 days before and after allogeneic HSCT. He developed transient non-severe hyperplastic gingivitis with a concomitant papulopustular skin rash.

Refer to the "Remarks" sections of the original guideline document for a discussion of the balance between benefits and harms for each of the interventions considered in the guideline.

Contraindications

Contraindications

Keratinocyte growth factor (KGF) is contraindicated in patients with known hypersensitivity to *Escherichia coli* derived proteins.

Qualifying Statements

Qualifying Statements

Not stated

Implementation of the Guideline

Description of Implementation Strategy

Considerations for Implementation

Clinical assessment for the presence and severity of oral mucositis should be a component of routine care for children receiving treatment for

cancer and undergoing haematopoietic stem cell transplantation (HSCT). Validated screening and assessment tools are important. A screening tool that includes mucositis has been developed but has not yet been validated. Validated mucositis assessment tools in paediatric patients include the Children's International Mucositis Evaluation Scale (ChIMES), the Oral Assessment Guide, the Oral Mucositis Assessment Scale and the Oral Mucositis Daily Questionnaire.

In this guideline, the Guideline Development Group identified three interventions that may be appropriate for mucositis prevention in children. Figure 3 (see the original guideline document) illustrates an algorithm for strategy implementation consideration. All three specific interventions (cryotherapy, low-level light therapy [LLLT] and keratinocyte growth factor [KGF]) evaluated in this clinical practice guideline were associated with a weak recommendation for use. Since all systematic reviews compared the intervention against placebo or no therapy, it may be helpful to compare the risk ratios (RRs) to gain insight into prioritisation. The RR against placebo or no therapy for LLLT, cryotherapy and KGF were 0.37, 0.46 and 0.81, respectively. In evaluating all three interventions, KGF is an intervention associated with high costs and a potential for harm. In contrast, cryotherapy is associated with very few costs and little risk of harm. On balance, if all three interventions are available, and clinically relevant, cryotherapy or LLLT should likely be prioritised for implementation whereas KGF should be used carefully in individual patients after weighing risks and benefits. There may also be important organizational and cost barriers to the adoption of LLLT since it requires specialised equipment and training for those who will administer therapy.

Dissemination of this guideline will be an important step in effective knowledge translation. The Guideline Development Group plans to disseminate this guideline through peer-reviewed publication, presentation at conferences and through paediatric oncology and dental organisations.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Sung L, Robinson P, Treister N, Baggott T, Gibson P, Tissing W, Wiernikowski J, Brinklow J, Dupuis LL. Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation. BMJ Support Palliat Care. 2015 Mar 27;:1-10. [50 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Mar 27

Guideline Developer(s)

Pediatric Oncology Group of Ontario - Professional Association

Source(s) of Funding

Funding support was provided by the Pediatric Oncology Group of Ontario. LS is supported by a New Investigator Award from the Canadian Institutes of Health Research (Grant no. 87719).

Guideline Committee

Pediatric Oncology Group of Ontario (POGO) Mucositis Prevention Guideline Development Group

Composition of Group That Authored the Guideline

Guideline Development Group Members: Lillian Sung, Division of Haematology/Oncology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; Paula Robinson, Pediatric Oncology Group of Ontario, Toronto, Ontario, Canada; Nathaniel Treister, Division of Oral Medicine and Dentistry, Brigham and Women's Hospital, Boston, Massachusetts, USA; Tina Baggott, Cancer Clinical Trials Office, Stanford University, Stanford, California, USA; Paul Gibson, Section of Hematology and Oncology, Children's Hospital, Western University, London, Ontario, Canada; Wim Tissing, Department of Pediatric Oncology/Hematology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; John Wiernikowski, Division of Pediatric Hematology/Oncology, McMaster University, McMaster Children's Hospital, Hamilton, Ontario, Canada; Jennifer Brinklow, Division of Pediatric Hematology/Oncology, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada; L. Lee Dupuis, Division of Haematology/Oncology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Financial Disclosures/Conflicts of Interest

Competing interests: None.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the BMJ Supportive & Palliative Care Web site .

Availability of Companion Documents

The following are available:

- Supplementary appendices 1-13 are available from the BMJ Supportive & Palliative Care Web site .
- Oberoi S, Zamperlini–Netto G, Beyene J, Treister NS, Sung L. Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis. PLoS ONE. 2014;9(9):e107418. Available from the PLOS One Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 21, 2016. The information was not verified by the guideline developer.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.